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Pesticide Assessment Guidelines, Subdivision F
Hazard Evaluation: Human and Domestic Animals
Series 85-1, General Metabolism
Addendum 7 on Data Reporting

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16. Abstract (Limit: 200 words)

The Data Reporting Guideline (DRG) for General Metabolism, Series 85-1, gives guidance to pesticide registrants on the format of their study report so that the Agency can review it efficiently. This guidance clarifies sections in the existing Pesticide Assessment Guidelines, Subdivision F, on data reporting. It provides an outline for the study report which data submitters can use in preparing their reports for submission to EPA to meet 40 CFR 158 data requirements for the registration of pesticides.

The DRG for Series 85-1, General Metabolism, is only one of a number of DRGs published by the National Technical Information Service as an addendum to Subdivision F of the Pesticide Assessment Guidelines.

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PB89-124085

PESTICIDE ASSESSMENT GUIDELINES

SUBDIVISION F

HAZARD EVALUATION DIVISION

HUMAN AND DOMESTIC ANIMALS

Series 85-1

General Metabolism

ADDENDUM 7 ON DATA REPORTING

Prepared by:

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Subdivision F - General Metabolism

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PESTICIDE ASSESSMENT GUIDELINES

HUMAN AND DOMESTIC ANIMALS

General Metabolism

Subdivision F, Series 81-4

DATA REPORTING

INTRODUCTION

A. Purpose

The purpose of the Guideline is to provide an example of an acceptable format for reporting materials, methods, and results of rat metabolism studies. These recommendations are intended to show how the requirements of §80-4, §85-1, and the Agency's Good Laboratory Practice Standards (40 CFR, Part 160) may be organized in a Final Report.

B. Objective

The objective of this document is to provide guidance to aid petitioners/registrants in generating reports that are compatible with the Agency's review process. While this guideline is not mandatory, petitioners and registrants are encouraged to submit complete reports that can be efficiently reviewed and evaluated by Agency scientists. This document pertains to organizing and presenting the substance of the data report. PR Notice 86-5, effective November 1, 1986, available from the Office of Pesticide Programs, US EPA, pertains to the physical formatting of reports (which are referred to as "studies") and submittal packages. Some of its requirements are mandatory.

RESPONSE TO PUBLIC COMMENTS

The purpose of this section is to acknowledge and address the questions and concerns expressed in letters received by the Agency in response to the public notice published in the FEDERAL REGISTER of May 25, 1988 (53 FR 18896). It should be emphasized that this Guideline is not intended to revise existing data requirements, but to provide for consistent and uniform reporting of toxicology data required to perform a scientifically sound hazard assessment and significantly reduce the time required to evaluate such data. The Agency has reviewed and evaluated the comments submitted by registrants regarding this Data Reporting Guideline (DRG). It has considered these comments and revised the document in response to some of these comments. Responses to specific comments are provided below.

1. Comment:

In section III. A. Test Substance under 1. c. Chemical composition, "The DRG calls for 'Qualitative and Quantitative Determination of its Chemical Composition.' .... believe this refers to radiochemical and/or chemical purity of the test substance and should be so stated."

Response:

Qualitative analysis by an acceptable technique is required prior to dosing to insure the identity of the test substance. Quantitative determination is required as an indication of purity.

2. Comment:

In 1. d. Impurities, "We seek clarification as to what level [of] ... trace impurities [need to] be identified. Identification of unknowns which are below the 1% level can be time consuming, laborious and add little to the study."

Response:

Type and quantities of trace impurities of one percent or higher are required. However, traces of lower magnitude are desired whenever practical and possible.

3. Comment:

In 2. b. Color, "It is suggested that the reference to 'color' be deleted because knowing the color of the test substance adds nothing to the study."

Response:

Although the color of the test substance may not seem to add much to the study, sometimes it can be used as an indicator of changes in the test substance.

4. Comment:

In 2. c. Solubility, "On the subject of solubility, a more meaningful requirement might be 'Gross Solubility in the Dosing Vehicle.' Knowing the solubility of the test substance in various solvents will do nothing for the study. In the case of the dosing vehicle, it is important to know whether the test substance was administered as a solution or a mixture. The variance of recoveries will be affected by the solubility of the dosing vehicle."

Response:

This section has been revised to read "Gross solubility in the vehicle solvent and/or partition coefficient."

5. Comment:

In 2. d. Stability, "We seek clarification as to what type of stability does the Agency want. Is it stability in the dosing vehicle; stability in storage; or other? Usually the test substance is added to the dosing vehicle immediately before use (generally less than one-half hour). This should be adequate control of stable and semi-stable test substances, i.e., if the test substance is stable in storage, then no additional testing of the dosing mixture/solution should be required."

Response:

This section is intented to provide information on the stability in storage and in the vehicle solvent. However, reference can also be made to this information in the "Product Chemistry" section in lieu of providing this information, if so preferred.

6. Comment:

Concerning the vehicle, "the type and composition of any vehicle is required. Determination of the composition of vehicles such as corn oil or complex emulsions will be an impossible task and should not be required. Perhaps the term 'type or description of any vehicle' would be better terminology for this requirement."

Response:

This section has been revised to read "type or description of any vehicle....."

7. Comment:

Concerning the starvation period, "It would seem that a description of the quarantine period would be more applicable and useful in the interpretation of a study. Information on the regimen for daily feeding can also be supplied."

Response:

To insure maximum absorption of the test substance, it is usually recommended that the animal be starved four to six hours prior to dosing. Additional information on the quarantine period or daily feeding regimen would also be useful in the review of the study.

8. Comment:

"Some elaboration should be given on the type of animal handling data which are required, i.e., quarantine period, dosing period, observation period, [and] sacrifice."

Response:

Information on animal handling should include quarantine period, observation period, type of caging, number of animals per cage, sacrifice and other relevant information.

9. Comment:

"It is strongly suggested to delete the requirement for cpm reporting since newer instruments automatically convert to dpm using an internal calibration curve. Cpm data in summary tables make the tables difficult to read and are not really meaningful. Radioactive counting data should be supplied as dpm or uci [sic] and should be consistent throughout the report. Summary tables employing both radioactive units (dpm or uci [sic]) and mass units (ug or mg equivalents), should be placed at the end of the report after any references. Small tables and figures which do not interrupt the flow of the text may be included in the main body of the report. An appendix can be used to include examples of conversion of cpm to dpm or uci [sic] values. In addition, the counting data, i.e., cpm, quench and chemiluminescence corrections, counting efficiency, etc., should all be archived in the raw data file, for potential raw data checks, and are thus not required in the formal report."

Response:

The requirement for cpm reporting has been deleted. However, information on counting efficiency must be provided. Summary tables employing both radioactive units (dpm or uCi), mass units (ug or mg equivalents), and figures should be included in the main body of the report whenever possible. The counting data should be appended to the report as described under Section VI of the DRG.

GUIDELINE

TITLE/COVER PAGE

Refer to PR Notice 86-5. Title page and additional requirements (i.e., requirements for data submission, Good Laboratory Practice, and statements of data confidentiality claims), if relevant to the study report, should precede the content of the study formatted below.

TABLE OF CONTENTS

A concise listing shall precede the body of the report, containing all essential elements of the study and the page and table number where the element is located in the final report of the study.

Essential elements of the table of contents should include a Summary, an Introduction, the Materials and Methods section, Results, Discussion/ Conclusions, References, Tables, Figures, Appendices, and key subsections as deemed appropriate. The table of contents should include the page number of each of these elements.

BODY OF THE REPORT

The body of the report shall include information required under Section 158.85(a) of Title 40 of the Code of Federal Regualtions, organized into sections and subsections as described below.

I. SUMMARY

As per §80-4(b)(1) of Subdivision F, this section of the study report shall contain a summary and analysis of the test results and a statement of the conclusions drawn from the analysis. This section should highlight the nature and magnitudue of metabolites, tissue residues, rate of clearance, bioaccumulation or bioretention, sex differences, etc. The summary should be presented in sufficient detail to permit independent evaluation of the findings.

II. INTRODUCTION

This section of the report should include the objective(s) of the study, Guideline references, regulatory history, if any, and a rationale.

III. MATERIALS AND METHODS

This section of the report shall include detailed descriptions of all elements including:

A. Test Substance

1. This subsection should include identification of the test substance, i.e.;

   a. Chemical name,
   b. Molecular structure,
   c. Qualitative and quantitative determination of its chemical composition, and
   d. Type and quantities of any trace impurities whenever possible.

2. This subsection should also include information on physical properties including;

   a. Physical state,
   b. Color,
   c. Gross solubility and/or partition coefficient, in addition to
   d. Stability.

3. The type or description of any vehicle, diluents, suspending agents, and emulsifiers or other materials used in administering the test substance should be stated.

4. If the test substance is radiolabeled, then information on the following should be included in this subsection;

   a. The type of radionuclide,
   b. Position of labeling,
   c. Specific activity, and
   d. Radiopurity.

B. Test Animals

This subsection should include information on the test animals including;

1. Species,
2. Strain,
3. Age,
4. Sex,
5. Body weight,
6. Health condition, and
7. Other relevant information.

C. Methods

This subsection should include details of the study design and methodology used. It should include a detailed description of;

1. How the dosing solution was prepared and the type of solvent used,
2. Number of treatment groups and number of animals per group,
3. Dosage level,
4. Dosage volume,
5. Route of administration,
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8. Total radioactivity per animal,
9. Animal handling,
10. Sample collection and frequency,
11. Sample handling,
12. Analytical methods used for separation,
13. Quantification/confirmation of metabolites, and
14. Other experimental measurements and procedures employed.

D. Statistical Analysis

If statistical analysis is used to analyze the study findings, then sufficient information on the method of analysis and the computer program employed should be included so that an independent reviewer/statistician can reevaluate and reconstruct the analysis.

IV. RESULTS

All data should be summarized and tabulated with appropriate statistical evaluation and placed in the text of this section. Radioactivity counting data should be summarized and presented as dpm, and ug or mg equivalents. Graphic illustrations of the findings, reproduction of the chromatographic and spectrometric charts, and proposed metabolic pathways and molecular structure of metabolites should be included in this section.

V. DISCUSSION AND CONCLUSION

1. In this section the author(s) should:

   a. Discuss the findings of the study in light of what is already known about this chemical or what is expected;

   b. Provide a plausible explanation of the metabolic pathways illustrated under "RESULTS";

   c. Emphasize species and sex differences whenever possible; and

   d. Compare nature and magnitude of metabolites, rate(s) of clearance, bioaccumulation or bioretention, and level of tissue residues in the single, low, high, and multidose groups.

2. The author(s) should be able to derive a concise conclusion that can be supported by the findings of this study.

VI. OPTIONAL SECTIONS

The author(s) may include additional sections such as appendices, bibliography, tables, and individual animal data.

PESTICIDE ASSESSMENT GUIDELINES

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HAZARD EVALUATION DIVISION

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General Metabolism

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